Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across Europe

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Abstract: Leptomeningeal metastases are a late manifestation of systemic cancer which affects up to 10% of patients with solid tumors. Prognosis is poor, and overall survival at 1 year is only approximately 10%. Management depends mainly on general and neurological condition, primary tumor, and patterns of metastasis, notably absence or presence of concurrent systemic or solid brain metastases. Here we set out to characterize current practice patterns of diagnosis and treatment of patients with leptomeningeal metastasis in Europe. We prepared a web-based survey including 25 simple or multiple choices questions on best practice supplemented by eight case vignettes with various diagnosis and management options. The survey was sent to the membership of the European Association of Neuro-Oncology and the European Organisation for Research and Treatment of Cancer Brain Tumor Group. Between April 7, 2016 and August 8, 2016, 224 colleagues from 26 countries initiated the survey, 115 colleagues completed the whole survey. There were major differences both in the general diagnostic and therapeutic approach, e.g., regarding the use of cerebrospinal fluid (CSF) flow studies, intra-CSF chemotherapy, various types of radiotherapy, and even more so when selecting decisions on diagnostic and therapeutic measures for single case vignettes. Diagnosis and treatment decisions for patients with leptomeningeal metastasis from solid tumors vary widely across Europe. Standardization of diagnosis and evaluation tools as well as controlled studies to improve the level of evidence for all therapeutic approaches to LM are required.

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Abstract

Background: Leptomeningeal metastases are a late manifestation of systemic cancer which affects up to 10% of patients with solid tumors. Prognosis is poor, and overall survival at one year is only approximately 10%. Management depends mainly on general and neurological condition, primary tumor, and patterns of metastasis, notably absence or presence of concurrent systemic or solid brain metastases. Here we set out to characterize current practice patterns of diagnosis and treatment of patients with leptomeningeal metastasis in Europe.

Methods: We prepared a web-based survey including 25 simple or multiple choices questions on best practice supplemented by 8 case vignettes with various diagnosis and management options. The survey was sent to the membership of the European Association of Neuro-Oncology (EANO) and the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor Group.

Results: Between April 7, 2016 and August 8, 2016, 224 colleagues from 26 countries initiated the survey, 115 colleagues completed the whole survey. There were major differences both in the general diagnostic and therapeutic approach, e.g., regarding the use of cerebrospinal fluid (CSF) flow studies, intra-CSF chemotherapy, various types of radiotherapy, and even more so when selecting decisions on diagnostic and therapeutic measures for single case vignettes.

Discussion: Diagnosis and treatment decisions for patients with leptomeningeal metastasis from solid tumors vary widely across Europe. Standardization of diagnosis and evaluation tools as well as controlled studies to improve the level of evidence for all therapeutic approaches to LM are required.

Key words

Leptomeningeal – metastasis – cerebrospinal – chemotherapy - intrathecal

Importance of the study

Leptomeningeal metastasis is typically a late and life-threatening complication from solid cancers. Diagnosis and management pathways are poorly standardized because of heterogeneous pretreatment and clinical presentation and because of a lack of data from randomized trials. In an effort to define the most important areas of consent versus dissent among neuro-oncologists in Europe, we performed a questionnaire-based survey to explore current standards of practice. The survey allowed to identify several areas of clinical research where more solid data are urgently needed to derive evidence-based guidelines for diagnosis and treatment: (i) the role of systemic pharmacotherapy in patients with isolated central nervous system disease, (ii) selection of patients for intra-CSF therapy and (iii) the integration of radiotherapy into multimodal treatment approaches.

Text

Introduction

Leptomeningeal metastasis is a serious complication of systemic cancer commonly occurring in later disease stages which affects approximately 10% of patients with solid tumors. The risk is highest for patients with breast cancer, lung cancer and melanoma. Survival at one year is ~~in the range of~~ approximately 10% and varies profoundly by primary tumor. Clinical evaluation, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis are the most important diagnostic measures [1]. Treatment recommendations vary mainly by primary tumor and pattern of brain and

meningeal disease, that is, e.g., the absence or presence of concurrent systemic or solid brain metastasis, the radiological presentation, and the absence or presence of tumor cells in the cerebrospinal fluid (CSF), and are typically rather individualized [2]. Many important questions regarding diagnosis and treatment of LM remain controversial and have never been explored in controlled clinical trials. Heterogeneous patterns of presentation, divergent modes of commonly heavy pretreatment, and poor prognosis are the main reasons why it has remained challenging to conduct prospective clinical trials in this patient population. Here we designed a questionnaire-based survey to explore the current routine clinical practice of diagnosing and treating LM and to identify the most important controversies to be addressed in future clinical trials across Europe.

Methods

A web-based survey containing 25 general questions on current practice patterns as well as 8 case presentations with diagnosis and management questions (Supplementary Note) was sent to members of the European Association of Neuro-Oncology (EANO) and of the Brain Tumor Group of the European Organisation for Research and Treatment of Cancer (EORTC) in April 2016 via the respective email listings of these organizations. The case vignettes are real patients from the authors` clinical practice and were selected based on their representation of primary cancers and the typical challenges associated with the diagnosis and treatment of LM from solid cancers. Responses were analysed with a focus on age and discipline of participants, physician in charge of LM at the center, and the number of LM patients seen per month. Comparisons between groups were done using Chi-square or Fisher exact test. Statistical analyses were performed with SAS Software, V9.4 (Cary, NC).

Results

General information

Between April 7, 2016 and August 8, 2016, a total of 224 colleagues from 26 countries initiated the survey and 115 colleagues completed the whole survey. Fifteen colleagues only opened the file without answering any of the questions. Rates of "no response" for the general questions varied between 8.5% and 15% with the exception on the question addressing the route of administration of intra-CSF therapy to which 23% of participants did not answer (Table).

Participants came mainly from France (n=35, 15.5%), Italy (n=28, 12.5%), Netherlands (n=22, 10%) and Spain (n=19, 8.5%) (Figure A), and the leading disciplines were neurology (n=77, 34%), medical oncology (n=52, 23%), radiation oncology (n=42, 19%) and neurosurgery (n=23, 10%) (Figure B). The age distribution was as follows: 31-40 years (n=56, 25%), 41-50 (n=69, 31%), 51-65 (n=76, 34%) (Supplementary Figure 1). ~~Three colleagues each were 30 years or younger, or older than 65; 17 participants did not indicate their age.~~ Hundred-nineteen participants (53%) indicated to see not more than 1 LM patient per month, 78 participants (35%) indicated to see 2-4 patients per month, and ~~only~~ 9 participants (4%) indicated to see 5 patients per month or more (Supplementary Figure 2). Almost no differences were observed between physicians in charge of 0-1 LM patients per month and physicians in charge of at least 2 patients per month among the different items of the survey.

One hundred-twenty nine participants (58%) felt that they were ~~the neuro-oncologist~~ in charge of LM at their institution (Supplementary Figure 3). Medical oncologists (54.5%) or neurologists (48%) were most often reported to be responsible

for the diagnosis of LM, whereas medical oncologists (63%) were more often in charge of treatment than neurologists (32%) or radiation oncologists (11%) (Figure C).

Diagnosis of LM

Only 36 participants (16%) indicated that a neurological scale was used to score the results of the neurological examination (Table). No difference was observed between neurologists and participants from other specialties (Supplementary Table). Only 51 colleagues (23%) reported that cerebrospinal MRI was not always done in patients with suspected LM. Similarly, only 64 participants (28.5%) reported that CSF flow studies were never done in the diagnostic work-up. However, a CSF flow study was reported to be always performed at LM diagnosis by significantly more participants not in charge of LM (24.5%) than by participants in charge of LM (13%) ($p=0.043$).

Only 125 participants (56%) indicated that CSF analysis was always performed as part of the diagnostic work-up in case of suspected LM from solid tumors whereas 78 participants (35%) indicated that CSF analysis was only done in case of doubt after clinical and MRI evaluation (Table). These numbers were much lower for suspected LM from gliomas, 39 participants (17.5%) versus 40 participants (18%). Radiation oncologists declared less often always performing a CSF cytology in case of suspicion of LM from solid tumors (26%) than neurologists (61%), medical oncologists (79%) or neurosurgeons (61%) ($p<0.0001$). ~~On the contrary, CSF analysis was indicated in case of doubt after clinical and MRI evaluation for LM from solid tumors mainly according to radiation oncologists (<0.0001).~~ Radiation oncologists also declared less frequently to perform CSF analysis (5%) in case of suspected LM from gliomas than other specialists (neurologists: 17%, medical oncologists: 23%, neurosurgeons: 17%) ($p=0.044$). The indication for CSF analysis for the diagnosis of LM varied significantly also by age.

~~Participants between 31-40 and 51-65 years declared more often than participants between 41-50 years to always perform CSF cytological analysis in case of suspicion of LM from solid tumors or from gliomas (p=0.0002, p=0.0015)~~ (Supplementary Table).

More than half (56.5%) of participants reported that CSF was processed within one hour. Interestingly, similar numbers of participants felt that a CSF cytology defined as atypical should be considered negative (40.5%) or positive (44.5%). In contrast, a CSF cytology defined as suspicious was considered positive by 167 participants (74.5%). Only 21 participants (9%) felt that a positive cytology was always required to diagnose LM (Table).

Treatment

The decision for systemic treatment was based on the primary cancer according to 126 participants (56%), but on CSF and MRI findings according to only 66 participants (29.5%), although multiple answers were allowed. Systemic treatment was declared being always administered when feasible by only 71 participants (31.5%) (Table). Systemic treatment was always recommended when feasible by medical oncologists in 50% and by neurosurgeons in 48%, as opposed to only 26% of radiation oncologists and 22% of neurologists (p=0.0029). The role of the primary tumor for systemic treatment was judged similar across disciplines (Supplementary Table).

The decision for intra-CSF treatment was again most often based on the primary cancer (n=126, 56%) but also on CSF and MRI findings (n=81, 36%) and depending on systemic treatment (n=68, 30.5%). Intra-CSF treatment was declared as being never administered by only 23 participants (10.5%) (Table). The indication for intra-CSF was determined by CSF and MRI characteristics for 47% of neurologists and 42% of medical oncologists, but only 30.5% of neurosurgeons and 21.5% of radiation oncologists

(p=0.039) (Supplementary Table). Almost half of the participants (103, 46%) selected intraventricular intra-CSF chemotherapy over intralumbar therapy ***only*** if repeated lumbar punctures were not feasible whereas 50 participants (22.5%) generally preferred intraventricular chemotherapy. Intraventricular intra-CSF chemotherapy was preferred over intralumbar administration for most patients by 31% of the participants in charge of LM versus only 12% of participants not in charge of LM (p=0.0025) (Table). No significant difference was observed between participants according to their specialties regarding the route of administration of intra-CSF chemotherapy (Supplementary Table).

Only 35 participants (15.5%) felt that WBRT should always be performed. WBRT was always recommended by 35% of neurosurgeons and 28.5% of radiation oncologists, but by only 14.5% of neurologists and 4% of medical oncologists (p=0.0012). WBRT was proposed in case of multifocal nodular disease by 73% of medical oncologists, 56% of neurologists, 50% of radiation oncologists and 39% of neurosurgeons (p=0.0248) (Supplementary Table).

Most participants (n=164, 73%) declared performing focal radiotherapy in LM patients in case of neurological symptoms only when these could be linked to MRI abnormalities. Only 30 participants (13.5%) agreed to opt for focal RT based on neurological symptoms only in LM patients (Table). Focal radiotherapy based on neurological symptoms in the presence of MRI abnormalities only was proposed mainly by radiation oncologists (90.5%) and medical oncologists (86.5%) as compared to neurologists (71.5%) and neurosurgeons (74%) (p=0.0401) (Supplementary Table).

Cerebrospinal MRI for follow-up was reported to be done routinely by 108 participants (48%), commonly ~~done~~ in 2 to 3 months intervals (60.5%) (Table). Standardized MRI follow-up was done more often when participants were in charge of LM (0.0406),

whereas 25.5% of participants in charge of LM and 45% of participants not in charge planned MRI only depending on clinical course. No significant difference was observed among participants from different specialties regarding the imaging follow-up. To define the response status, 120 participants (53.5%) reported that they considered changes in steroid dose. Change of steroids dose was considered as part of criteria for response assessment of LM by 81% of medical oncologists, 62.5% of radiation oncologists, 56.5% of neurosurgeons and 50.5% of neurologists (p=0.0071) (Supplementary Table).

Case vignettes

Eight cases were proposed to explore the diagnosis and treatment strategies in distinct situations (Supplementary Note 1): non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR) wildtype (case 1) and EGFR mutated (case 5); melanoma, BRAF mutated (case 2); breast cancer, HER2-negative (case 3) and HER2-positive (case 4); medulloblastoma (case 6); glioblastoma (case 7) and ependymoma (case 8). The completion rate was lower than for the general questionnaire with the following percentages of “no response”: case 1: 37.5%; case 2: 40-47.5%; case 3: 46-61%; case 4: 48-50.5%; case 5: 55-66%; case 6: 59%-64.5%, case 7: 57-60.5% and case 8: 55.5-60%). The highest rates of non-response within each case were observed when participants had to select a systemic agent.

Cases 2 and 5 addressed the initial evaluation of LM. Most participants agreed on the role of completing the initial evaluation of LM with an entire spinal MRI when lesions were first diagnosed in the brain. Only a minority of participants performed CSF flow studies at diagnosis. For most cases, no clear consensus was observed for treatment recommendations. However, most participants agreed on the value of combining therapeutic options. WBRT was recommended most of the time in

combination with systemic treatment and/ or intra-CSF in case of diffuse linear cerebral involvement (cases 2 and 3). However, WBRT was not recommended in the absence of brain involvement on cerebral MRI (case 4). Systemic treatment was widely proposed in almost all cases, with the exception of ependymoma (case 8), but without consensus on the choice of agent (cases 2, 5, 6, 8), with the exception of capecitabine for LM from breast cancer LM (case 3) and of a nitrosourea for LM from glioblastoma (case 7). Half of the participants recommended intra-CSF chemotherapy in non-brain primary tumors with LM, but almost no intra-CSF therapy was suggested for LM from medulloblastoma (case 6), glioblastoma (case 7) or ependymoma (case 8). Intra-CSF chemotherapy was mostly recommended in the presence of tumor cells in the CSF, but also when CSF cytology was negative (case 1). Liposomal cytarabine and methotrexate were the 2 intra-CSF drugs most commonly chosen.

Discussion

The diagnosis of LM remains difficult and is defined in most recent cohorts by the presence of malignant cells in the CSF or, in the absence of malignant cells in the CSF, by concomitant characteristic clinical symptoms or signs and typical MRI findings [3-16]. However, clinical symptoms and signs vary according to areas of the CNS involved by tumor cells and may be difficult to distinguish from other neurological signs in cancer patients that are not related to LM.

In this survey, we observed that only a minority (16%) of participants used a scale for the neurological evaluation, although recommended by the Response Assessment in Neuro-Oncology (RANO) – Leptomeningeal Metastasis (LM) group [1].

We also noted that neurologists or medical oncologists do not use a neurological scale more frequently than neurosurgeons or radiation oncologists for the clinical evaluation. Such a scale could help defining the neurological signs related to LM and to detect changes in the neurological status during follow-up and should be considered for clinical practice.

Surprisingly, 23% of the participants declared not to perform a cerebrospinal MRI in case of suspicion of LM, although LM may involve both brain and spine and although the radiological presentation should have an impact on the clinical decision making [2]. Moreover, not performing a complete baseline evaluation renders response assessment difficult. Sixty-four participants (28.5%) declared that an evaluation of CSF flow was never done at diagnosis. Mainly physicians who had declared not being in charge of LM in their respective hospitals proposed CSF flow studies. In most recent cohorts, including patients receiving intra-CSF chemotherapy, no CSF flow data are reported [3-21] although recommended by the RANO-LM group for patients considered for intra-CSF treatment [1].

Only half of the participants (56%) reported that CSF analysis was always done when LM from solid tumors except glioma is suspected, and up to 80% reported to perform CSF analyses only in case of doubt after clinical and MRI evaluation. Until now, despite a sensitivity rate of only 66-90% in recent cohorts of LM patients [4-9,15,22], the gold standard for the diagnosis of LM remains the demonstration of tumor cells in the CSF since clinical and MRI findings can be typical, but never specific. The prognostic role of malignant cells in the CSF at baseline and their role in the response assessment has not been clearly defined [1]. However, the identification of malignant cells in the CSF may influence the therapeutic decision, especially for intra-CSF treatment, which has a 1-2 mm limited penetration into tumoral nodules and acts probably mainly on

floating cells and linear contrast enhancement. Only 17.5% of participants declared to perform always a CSF analysis in case of suspicion of LM in glioma patients. This may be explained by the limited role of intra-CSF chemotherapy within the overall treatment strategy.

Radiation oncologists declared to perform less often ~~systematic~~ CSF analyses when LM is suspected. CSF volume and time between sampling and processing determine the quality of CSF samples and impact the sensitivity of CSF analysis [1,23,24,25]. When CSF analysis was performed, the median volume of CSF was declared as more than 5 ml by 55.5% of participants and between 2 and 5 ml by 30.5% of participants, and the median time between CSF sampling and processing was declared as less than 60 minutes in 56.5%, and in less than 90 minutes in 77.5%, which reflects broad acceptance of these recommendations.

Another important point concerns the interpretation of the results of CSF analyses. For 44.5% of participants, “atypical” CSF is usually considered as positive and for 74.5% of participants, “suspicious” CSF is considered as positive. In the RANO-LM recommendations, an “atypical” CSF should be considered as negative and a “suspicious” CSF as positive [1]. These definitions have not been clearly defined by pathologists and have not been integrated into routine practice yet.

Several approaches can be combined for the treatment of LM. Systemic treatment is always administered by 31.5% of participants, and intra-CSF treatment is always given only by a minority or participants (3.5%). For others, decisions for systemic or intra-CSF treatment mainly depend on the primary cancer or on CSF and MRI findings. Intraventricular administration of chemotherapy was preferred over intralumbar administration for most patients only by 22.5% of participants whereas the majority reported to use a ventricular device only when lumbar punctures are not

feasible. No difference was observed for the route of administration of intra-CSF treatment according to the specialty of participants, but intraventricular route of administration was preferred by participants declared as being in charge of LM. This is probably because ventricular devices permit, through a rapid painless and safe procedure, a homogeneous distribution of the drug into the CSF [26,27,28].

WBRT was proposed for all LM cases by 15.5% of participants and most participants suggested WBRT in case of concomitant brain metastases or multifocal nodular disease. Importantly, participants declared to administer focal radiotherapy mainly when neurological symptoms were associated with MRI abnormalities and not for neurological symptoms or signs alone.

In this survey, treatment approach varied significantly according to specialty by training. Half of the medical oncologists recommended ~~a~~ systemic treatment ~~approach~~ whenever ~~always when~~ feasible versus a quarter of radiation oncologists. Moreover, a third of radiation oncologists always recommended WBRT versus less than 5% of medical oncologists.

Until now, only a few randomized trials in LM have been published, the last one more than 10 years ago [29-34]. Pretreatment evaluation, response assessment and the reporting of treatment-related toxicity varied widely in these studies [35]. Thus no strong recommendations can be established for the management of LM, and treatment options remain mainly based on expert opinion.

In this survey, only 48% of the participants declared performing a cerebrospinal MRI for the follow-up of their patients regularly, and in up to 28.5% only depending on the clinical course. More cerebrospinal MRI were recommended during the follow-up of patients by participants in charge of LM presumably because these colleagues

recognize the significance of the craniospinal extension of LM. No difference by specialty was observed for the frequency of MRI evaluation during follow-up.

Steroid doses were used as part of criteria to define the response to treatment as in brain metastases and gliomas for 53.5% of participants. The efficacy of steroids in the management of LM remains controversial, and the RANO-LM group proposed to not consider steroids in the response criteria for LM related to solid tumors [1].

The optimal management of LM requires multidisciplinary care and diagnosis and treatment strategies should ideally be developed in tumor boards. Although we did not ask specifically for that, we suspect that LM patients are often no finally discussed in such boards because organ specialists for the most common primary tumors breast, lung and melanoma may not share tumor boards with the dedicated neuro-oncology teams. This is why individual physicians and their attitudes as explored here are very important.

We are aware of several limitations of this study: The number of participants was limited, 51% colleagues terminated after opening the survey, presumably because of the length of the survey. The poor response rate for some questions may also reflect uncertainties of many collegues and the, the lack of consensus for the management of the disease. That mainly physicians treating only one patient per month participated, may seem to challenge the validity of the results, but their responses did overall not differ from responses of colleagues who reported to see more patients. Since participants were not systematically approached, the validity of the answers still remains uncertain as the results represent what clinical report [36]. Finally, the survey focused on diagnosis and therapeutic options and missed the opportunity to explore the current practice of palliative care for LM patients.

~~In conclusion, there are too few clinical trials data to derive evidence-based recommendations for diagnosis and treatment of LM from solid tumors.~~ Nevertheless, this survey ~~informs on~~ addresses important topics for preparing institutional or national guidelines for the diagnosis and management of patients with LM from solid tumors and helps to identify areas of controversies which can be addressed in future clinical trials.

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Does not apply

Conflict related to this work

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MW: no conflict of interest

Figure legend

Figure. **Characteristics of participants.** Distribution per country (A), per discipline (B) and per self-assessed role in the management of LM per discipline (C). In B, other disciplines indicated were: biologists (n=1, 0.5%), neuro-oncologists (n=3, 1%), neuropathologist (n=2, 1%); pediatric neurologist (n=2, 1%), radiologist (n=1, 0.5%). For C, there are no responses for diagnosis by 24 participants (11%) and for treatment by 22 participants (10%).

References

1. Chamberlain M, Junck L, Brandsma et al. Leptomeningeal Metastases: A RANO proposal for response criteria. Neuro Oncol. 2016 Dec 29. pii: now183. doi: 10.1093/neuonc/now183.

2. Le Rhun E, Galanis E (2016) Leptomeningeal metastases of solid cancer. Curr Opin Neurol 29:797–805. doi: 10.1097/WCO.0000000000000393

3. Regierer AC, Stroux A, Kühnhardt D, et al (2008) Contrast-Enhancing Meningeal Lesions Are Associated with Longer Survival in Breast Cancer-Related Leptomeningeal Metastasis. Breast Care Basel Switz 3:118–123. doi: 10.1159/000121688

4. Gauthier H, Guilhaume MN, Bidard FC, et al (2010) Survival of breast cancer patients with meningeal carcinomatosis. Ann Oncol Off J Eur Soc Med Oncol ESMO 21:2183–2187. doi: 10.1093/annonc/mdq232

5. Lee S, Ahn HK, Park YH, et al (2011) Leptomeningeal metastases from breast cancer: intrinsic subtypes may affect unique clinical manifestations. Breast Cancer Res Treat 129:809–817. doi: 10.1007/s10549-011-1682-0

6. de Azevedo CRAS, Cruz MRS, Chinen LTD, et al (2011) Meningeal carcinomatosis in breast cancer: prognostic factors and outcome. J Neurooncol 104:565–572. doi: 10.1007/s11060-010-0524-y

7. Yust-Katz S, Garciarena P, Liu D, et al (2013) Breast cancer and leptomeningeal disease (LMD): hormone receptor status influences time to development of LMD

and survival from LMD diagnosis. J Neurooncol 114:229–235. doi: 10.1007/s11060-013-1175-6

8. Le Rhun E, Taillibert S, Zairi F, et al (2013) A retrospective case series of 103 consecutive patients with leptomeningeal metastasis and breast cancer. J Neurooncol 113:83–92. doi: 10.1007/s11060-013-1092-8

9. Abouharb S, Ensor J, Loghin ME, et al (2014) Leptomeningeal disease and breast cancer: the importance of tumor subtype. Breast Cancer Res Treat 146:477–486. doi: 10.1007/s10549-014-3054-z

10. Morris PG, Reiner AS, Szenberg OR, et al (2012) Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer 7:382–385. doi: 10.1097/JTO.0b013e3182398e4f

11. Umemura S, Tsubouchi K, Yoshioka H, et al (2012) Clinical outcome in patients with leptomeningeal metastasis from non-small cell lung cancer: Okayama Lung Cancer Study Group. Lung Cancer Amst Neth 77:134–139. doi: 10.1016/j.lungcan.2012.03.002

12. Gwak H-S, Joo J, Kim S, et al (2013) Analysis of treatment outcomes of intraventricular chemotherapy in 105 patients for leptomeningeal carcinomatosis from non-small-cell lung cancer. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer 8:599–605. doi: 10.1097/JTO.0b013e318287c943

13. Riess JW, Nagpal S, Iv M, et al (2014) Prolonged survival of patients with non-small-cell lung cancer with leptomeningeal carcinomatosis in the modern treatment era. Clin Lung Cancer 15:202–206. doi: 10.1016/j.cllc.2013.12.009

14. Kuiper JL, Hendriks LE, van der Wekken AJ, et al (2015) Treatment and survival of patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: A retrospective cohort analysis. Lung Cancer Amst Neth 89:255–261. doi: 10.1016/j.lungcan.2015.05.023

15. Harstad L, Hess KR, Groves MD (2008) Prognostic factors and outcomes in patients with leptomeningeal melanomatosis. Neuro-Oncol 10:1010–1018. doi: 10.1215/15228517-2008-062

16. Geukes Foppen MH, Brandsma D, Blank CU, et al (2016) Targeted treatment and immunotherapy in leptomeningeal metastases from melanoma. Ann Oncol Off J Eur Soc Med Oncol ESMO 27:1138–1142. doi: 10.1093/annonc/mdw134

17. Rudnicka H, Niwińska A, Murawska M (2007) Breast cancer leptomeningeal metastasis--the role of multimodality treatment. J Neurooncol 84:57–62. doi: 10.1007/s11060-007-9340-4

18. Niwińska A, Rudnicka H, Murawska M (2013) Breast cancer leptomeningeal metastasis: propensity of breast cancer subtypes for leptomeninges and the analysis of factors influencing survival. Med Oncol Northwood Lond Engl 30:408. doi: 10.1007/s12032-012-0408-4

19. Meattini I, Livi L, Saieva C, et al (2012) Prognostic factors and clinical features in patients with leptominengeal metastases from breast cancer: a single center experience. J Chemother Florence Italy 24:279–284. doi: 10.1179/1973947812Y.0000000034

20. Lara-Medina F, Crismatt A, Villarreal-Garza C, et al (2012) Clinical features and prognostic factors in patients with carcinomatous meningitis secondary to breast cancer. Breast J 18:233–241. doi: 10.1111/j.1524-4741.2012.01228.x

21. Park JH, Kim YJ, Lee J-O, et al (2012) Clinical outcomes of leptomeningeal metastasis in patients with non-small cell lung cancer in the modern chemotherapy era. Lung Cancer Amst Neth 76:387–392. doi: 10.1016/j.lungcan.2011.11.022

22. Kwon J, Chie EK, Kim K, et al (2014) Impact of multimodality approach for patients with leptomeningeal metastases from solid tumors. J Korean Med Sci 29:1094–1101. doi: 10.3346/jkms.2014.29.8.1094

23. Glantz MJ, Cole BF, Glantz LK, et al (1998) Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. Cancer 82:733–739.

24. Rogers LR, Duchesneau PM, Nunez C, et al (1992) Comparison of cisternal and lumbar CSF examination in leptomeningeal metastasis. Neurology 42:1239–1241.

25. Dux R, Kindler-Röhrborn A, Annas M, et al (1994) A standardized protocol for flow cytometric analysis of cells isolated from cerebrospinal fluid. J Neurol Sci 121:74–78.

26. Zairi F, Le Rhun E, Bertrand N, et al (2015) Complications related to the use of an intraventricular access device for the treatment of leptomeningeal metastases from solid tumor: a single centre experience in 112 patients. J Neurooncol. doi: 10.1007/s11060-015-1842-x

27. Kennedy BC, Brown LT, Komotar RJ, McKhann GM (2016) Stereotactic catheter placement for Ommaya reservoirs. J Clin Neurosci Off J Neurosurg Soc Australas 27:44–47. doi: 10.1016/j.jocn.2015.11.005

28. Morgenstern PF, Connors S, Reiner AS, Greenfield JP (2016) Image guidance for the placement of Ommaya reservoirs: A comparison of fluoroscopy and frameless stereotactic navigation in 145 patients. World Neurosurg. doi: 10.1016/j.wneu.2016.04.090

29. Hitchins RN, Bell DR, Woods RL, Levi JA (1987) A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J Clin Oncol Off J Am Soc Clin Oncol 5:1655–1662.

30. Grossman SA, Finkelstein DM, Ruckdeschel JC, et al (1993) Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. J Clin Oncol Off J Am Soc Clin Oncol 11:561–569.

31. Glantz MJ, Jaeckle KA, Chamberlain MC, et al (1999) A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal

methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res Off J Am Assoc Cancer Res 5:3394–3402.

32. Boogerd W, van den Bent MJ, Koehler PJ, et al (2004) The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. Eur J Cancer Oxf Engl 1990 40:2726–2733. doi: 10.1016/j.ejca.2004.08.012

33. Shapiro WR, Schmid M, Glantz M, Miller JJ (2006) A randomized phase III/IV study to determine benefit and safety of cytarabine liposome injection for treatment of neoplastic meningitis. ASCO Meet Abstr 24:1528.

34. Glantz MJ, LaFollette S, Jaeckle KA, et al (1999) Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. J Clin Oncol Off J Am Soc Clin Oncol 17:3110–3116. doi: 10.1200/jco.1999.17.10.3110

35. Chamberlain M, Soffietti R, Raizer J, et al (2014) Leptomeningeal metastasis: a Response Assessment in Neuro-Oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro-Oncol 16:1176–1185. doi: 10.1093/neuonc/nou089

36. Abrey LE, Louis DN, Paleologos N, Lassman AB, Raizer JJ, Mason W, Finlay J, Mac Donald DR, De Angelis LM, Cairncross JG; Oligodendroglioma Study Group. Survey of treatment recommendations for anaplastic oligodendroglioma. Neuro-Oncol 9(3):314-318. Epub 2007 Apr 13.

Table. Responses to the general questions on current practice of diagnosing and treating LM

DIAGNOSIS	Number (% of participants)
At your institution, a standardized neurological scale to score neurological symptoms/signs is performed for the management of LM?	yes: 36 (16%) no: 165 (74%) no response: 23 (10%)
At your institution, a cerebrospinal MRI is always performed regardless of localizing neurologic symptoms / signs in suspected LM:	yes: 153 (68%) no: 51 (23%) no response: 20 (9%)
At your institution, a CSF flow study is performed for the diagnosis of LM from solid tumors other than gliomas:*	always : 36 (16%) depending on patient's characteristics: 62 (27.5%) depending on disease's characteristics: 69 (31%) in case of toxicity of the intra-CSF treatment: 6 (2.5%) never: 64 (28.5%) no response: 21 (9.5%)
At your institution, a CSF analysis is done (in cases without contra-indication):*	always in case of suspicion of LM from solid tumors other than glioma: 125 (56%) always in case of suspicion of LM from glioma (not other solid tumors): 39 (17.5%) only in case of doubt after clinical and MRI evaluation for solid tumors other than glioma: 78 (35%) only in case of doubt after clinical and MRI evaluation for glioma: 40 (18%) no response: 19 (8.5%)
At your institution, what is the median volume of CSF sample collected?	0-2 ml: 3 (1.5%) 2-5 ml: 68 (30.5%) 5-10 ml: 86 (38%) >10 ml: 39 (17.5%) no response: 28 (12.5%)

At your institution, what is the median time between CSF sampling and processing?	<30 minutes: 36 (16%) 30-60 minutes: 91 (40.5%) 60-90 minutes: 47 (21%) >90 minutes: 20 (9%) no response: 30 (13.5%)
At your institution, a CSF cytology defined as «atypical» is usually considered:	positive: 100 (44.5%) negative: 91 (40.5%) no response: 33 (15%)
At your institution, a CSF cytology defined as «suspicious» is usually considered:	positive: 167 (74.5%) negative: 28 (12.5%) no response: 29 (13%)
At your institution, is positive CSF cytology is always required to diagnose LM?	yes: 21 (9%) no: 181 (81%) no response: 22 (10%)
In case of negative CSF cytology, a combination of clinical and radiological findings is considered sufficient to diagnose LM?	yes: 191 (85%) no: 11 (5%) no response: 22 (10%)

TREATMENT – FOLLOW UP	Number (%)
At your institution, systemic treatment for LM is administered:*	always when feasible: 71 (31.5%) never: 2 (1%) depending on CSF and MRI findings: 66 (29.5%) depending on the primary cancer: 126 (56%) depending on molecular data of the primary cancer: 35 (15.5%) only in combination with intra-CSF treatment: 10 (4.5%) no response: 23 (10.5%)
At your institution, intra-CSF treatment	always: 8 (3.5%)

for LM is administered:*	never: 23 (10.5%) depending on CSF and MRI findings: 81 (36%) depending on the primary cancer: 126 (56%) depending on molecular data of the primary cancer: 28 (12.5%) depending on the systemic treatment: 68 (30.5%) only in combination with a systemic treatment: 12 (5.5%) no response: 25 (10.5%)
At your institution, intraventricular intra-CSF chemotherapy is preferred over intralumbar intra-CSF chemotherapy:*	for most patients: 50 (22.5%) only in patients with regular CSF flow studies: 15 (6.5%) only when no WBRT is given: 9 (4%) only if repeated lumbar punctures are not feasible: 103 (46%) only if patients require anticoagulation: 10 (4.5%) no response: 51 (23%)
At your institution, WBRT is performed:*	always: 35 (15.5%) in case of concomitant BM only : 108 (48%) in case of nodular/bulky LM disease: 115 (51.5%) never: 4 (2%) no response: 27 (12%)
At your institution, in a patient with a diagnosis of LM and a predominant symptomatic site (i.e. cauda equina, posterior fossa, skull base) you perform focal RT based on:	neurological symptoms only: 30 (13.5%) neurological symptoms only when associated with MRI abnormalities: 164 (73%) no response: 30 (13.5%)
At your institution, a cerebro-spinal MRI is always performed in the follow-up regardless of signs:	yes: 108 (48%) no: 92 (41%) no response: 24 (11%)
At your institution, what is the frequency of MRI examination in the follow-up?	every 2 months: 30 (13.5%) every 2 months initially, then every 3 months: 54 (24%) every 3 months: 51 (23%) only depending on the clinical course: 64 (28.5%) no response: 25 (11%)

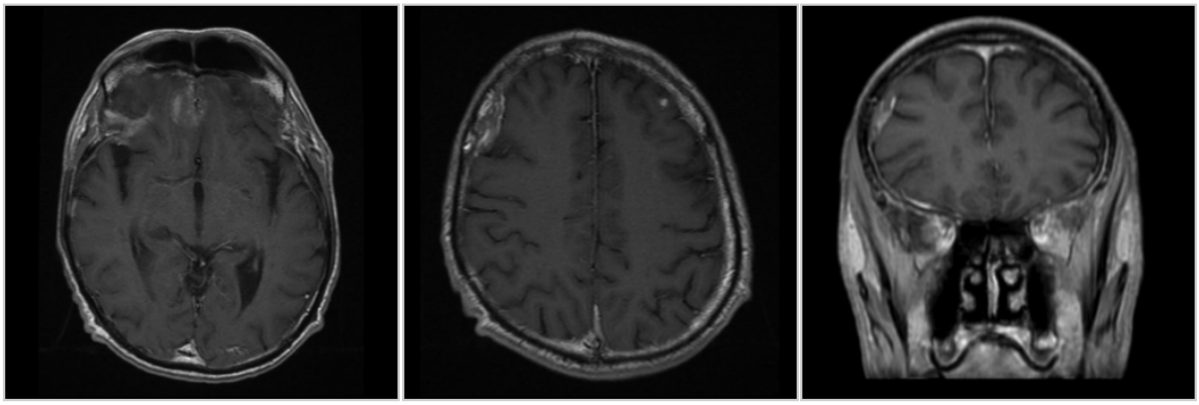
At your institution, the change of steroid doses following antineoplastic treatment is part of criteria for defining response or progression (as in brain metastases and malignant gliomas):	yes: 120 (53.5%) no: 79 (35.5%) no response: 25 (11%)

* multiple answers were allowed

Case 1 NON-SMALL CELL LUNG CANCER, EGFR WILD TYPE

59 year-old male at the time of neurological evaluation, coronaropathy and severe atheroma of cervical and femoral arteries

- January 2012 : lung adenocarcinoma, EGFR negative, pT2b pN1 M0
- February 2012 : lung + axillary resection followed by cisplatin + vinorelbine X 4 cycles
- August 2015 : mediastinal lymph nodes progression ➔ local radiotherapy, then carboplatin + paclitaxel
- November 2015 : repeated falls leading to a brain MRI showing both brain and meningeal lesions. Spinal MRI: no CNS metastases. Normal neurological examination. Stable extracerebral disease



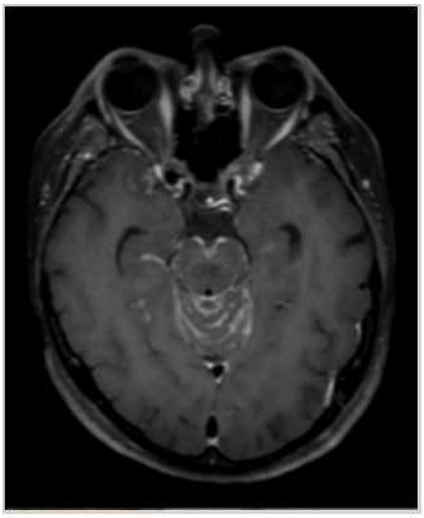
Question 1 : if the CSF is negative, what would be your recommendation for the treatment of the patient ?	Number (%)
whole brain radiotherapy	42 (19%)
whole brain radiotherapy followed by systemic treatment	64 (28.5%)
whole brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy	15 (6.5%)
stereotactic radiotherapy	3 (1.5%)
stereotactic brain radiotherapy followed by systemic treatment	10 (4.5%)
stereotactic brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy	4 (2%)
systemic treatment alone	2 (1%)
systemic treatment and intra-CSF chemotherapy	6 (2.5%)
intra-CSF chemotherapy alone	1 (0.5%)
other	3 (1.5%)
no answer	74 (33%)

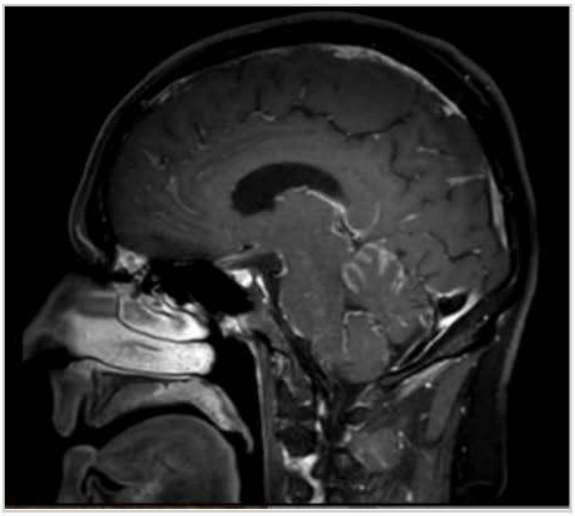
Question 2 : if the CSF is positive, what would be your recommendation for the treatment of the patient ?	Number (%)
whole brain radiotherapy	24 (10.5%)
whole brain radiotherapy followed by systemic treatment	42 (18.75%)
whole brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy	43 (19%)
stereotactic radiotherapy	2 (1%)
stereotactic brain radiotherapy followed by systemic treatment	0 (0%)
stereotactic brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy	7 (3%)
systemic treatment alone	4 (2%)
systemic treatment and intra-CSF chemotherapy	8 (4%)
intra-CSF chemotherapy alone	1 (0.5%)
WBRT plus intra-CSF chemotherapy	2 (1%)
other	16 (7%)
no answer	75 (22.5%)

Case 2 MELANOMA, BRAF-MUTATED

38 year-old male at the time of neurological evaluation

- May 2004 : nodular achromomatic dorsal melanoma, Clark IV, BRAF-mutated
- June 2004 to April 2007 : inclusion in a clinical trial of vaccinotherapy with ganglioside
- September 2007 : left axillary lymph node metastases, surgery (axillary resection) followed by radiotherapy
- June 2011 : right axillary lymph node metastases, surgery (axillary resection)
- May 2013 : lymph nodes, lung, spleen, liver metastases ➔ inclusion in an anti-RAF/anti-MEK clinical trial, vemurafenib arm, with a complete response
- September 2014 : brain metastases ➔ temozolomide
- November 2014 : isolated progression of the brain metastases ➔ dabrafenib
- July 2015 : progression of one isolated brain metastasis ➔ SRS by gammaknife, followed by dabrafenib + pembrolizumab
- October 2015 : leptomeningeal lesions on brain MRI, with malignant cells in the CSF. Good general status (ECOG-PS=0), normal neurological examination. no systemic progression





Question 1 : how would you complete the initial evaluation ?	Number (%)
entire spinal MRI	110 (49%)
CSF flow study	42 (17.75%)
no more examination	18 (8%)
other	2 (1%)
no answer	90 (40%)

Question 2 : which option would you recommend for the management of the patient ?
whole brain radiotherapy
whole brain radiotherapy followed by systemic treatment
whole brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy
systemic treatment alone
systemic treatment and intra-CSF chemotherapy
intra-CSF chemotherapy alone
whole brain radiotherapy plus intra-CSF chemotherapy
other
no answer

Question 3 : which systemic treatment would you choose ?	Number (%)
fotemustine	14 (6%)
ipilimumab	19 (8.5%)
dabrafenib + ipilimumab	21 (9.5%)
nivolumab	38 (17%)
other	26 (11.5%)
no answer	106 (47.5%)

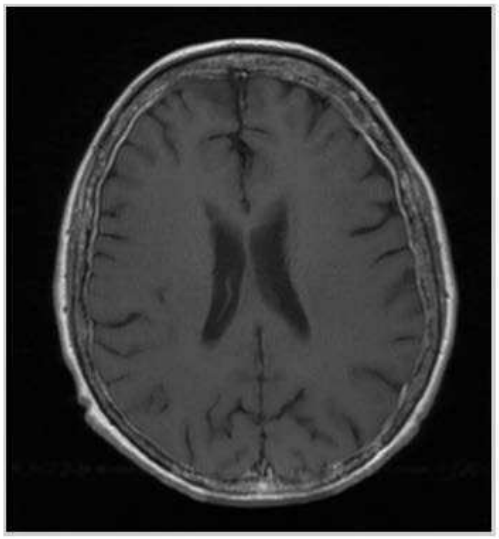
Question 4 : Which agent would you use for intra-CSF chemotherapy?	Number (%)
liposomal cytarabine	36 (16%)
methotrextate	32 (14.5%)
thiotepa	5 (2%)
I never use intra-CSF chemotherapy	39 (17.5%)
other	10 (4%)
no answer	102 (46%)

Case 3 BREAST CANCER, HER2 NEGATIVE

49 year-old at the time of neurological evaluation

- 2002 : left invasive ductal carcinoma, ER-positive, PR-positive, HER2-negative
- 2002 : surgery (mastectomy, axillary resection), chemotherapy (5-fluorouracil-epirubicine-cyclophosphamide – FEC 50), hormonotherapy (tamoxifen)
- 2005 : loco-regional recurrence ➔ surgery, chemotherapy (3 FEC100, 3 docetaxel), radiotherapy, LH-RH analogue (triptoreline)
- January 2007 : left axillary recurrence ➔ capecitabine, surgery, axillary radiotherapy, triptoreline + arimidex
- January 2008 : lymph nodes and pulmonary progression ➔ paclitaxel + bevacizumab followed by maintenance bevacizumab and triptoreline
- December 2009 : pulmonary progression ➔ paclitaxel + bevacizumab followed by maintenance bevacizumab
- January 2011 : pulmonary progression ➔ paclitaxel + bevacizumab
- September 2011 : severe neuropathy leading to an interruption of the treatment ➔ fulvestrant + triptoreline
- September 2013 : local pulmonary progression ➔ cyberknife + fulvestrant + triptoreline

- June 2014 : isolated cerebellar metastasis (no progression of the extracerebral disease), surgery, fossa posterior radiotherapy, fulvestrant + triptoreline
- April 2015 : brain and spinal MRI with diffuse linear contrast enhancement ; neurological evaluation : mild reduction of visual acuity, left tinnitus, mild gait disorders, mild left lower limb deficit and numbness, urinary incontinence ; CSF analysis : presence of malignant cells. No progression of the extraCNS disease



Question 1 : which option would you recommend for the management of the patient ?	Number (%)
whole brain radiotherapy	1 (0.5%)
whole brain radiotherapy followed by systemic treatment	7 (3%)
whole brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy	3 (1.5%)
whole brain radiotherapy and cauda equina radiotherapy followed by systemic treatment	26 (11.5%)
whole brain radiotherapy and cauda equina radiotherapy followed by systemic treatment and intra-CSF chemotherapy	14 (6.25%)
cauda equina radiotherapy followed by systemic treatment	18 (8%)
cauda equina radiotherapy followed by systemic treatment and intra-CSF chemotherapy	0 (0%)
systemic treatment alone	6 (2.5%)
systemic treatment and intra-CSF chemotherapy	22 (10%)

intra-CSF chemotherapy alone	18 (8%)
other	6 (2.5%)
no answer	103 (46%)

Question 2 : which systemic treatment would you choose ?	Number (%)
capecitabine	33 (14.5%)
paclitaxel	6 (2.5%)
FEC 50	2 (1%)
vinorelbine	14 (6.5%)
gemcitabine	12 (5.5%)
other	20 (9%)
no answer	137 (61%)

Question 3 : which intra-CSF agent would you use, if this therapeutic agent was available, and if leptomeningeal metastasis is confirmed:	Number (%)
liposomal cytarabine	38 (17%)
methotrextate	43 (19%)
thiotepa	2 (1%)
I never use intra-CSF chemotherapy	16 (7%)
other	7 (3%)
no answer	118 (53%)

Case 4 BREAST CANCER, HER2 POSITIVE

62 year-old woman at the time of neurological evaluation.

- 1996: right invasive ductal carcinoma (ER 9%, PR 31%)
- 1996: surgery (mastectomy, axillary resection) and hormone therapy (aromatase inhibitors)
- January 2015: slow onset of back pain and radicular pain L5-S1 on the right side, followed by weakness of legs and urinary incontinence over the next months
- June 2015: spinal MRI with multiple nodular enhancing lesions from L1 to S1 in the leptomeninges (Fig. A); brain MRI: no abnormalities; CSF examination: neoplastic cells and modest protein content increase

- July 2015: Laminectomy with resection of the bulky lesion : histological confirmation of breast carcinoma (ER-negative, PR-negative, HER2 3+)

Fig. A

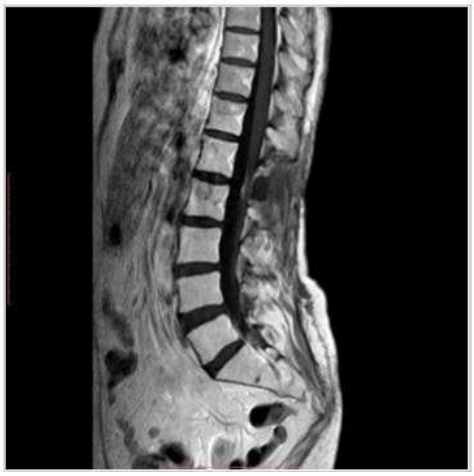


Fig. B

Question 1 : what treatment would you choose if brain MRI is normal ?
radiotherapy of the lumbar spine only
systemic therapy (based on trastuzumab or another anti-HER2 agent)
intrathecal chemotherapy only (either methotrexate or liposomal cytarabine)
combination of lumbar radiotherapy and either systemic or intrathecal therapy
combination of whole brain and lumbar radiotherapy and either systemic or intrathecal therapy
whole brain radiotherapy and either systemic or intrathecal therapy
other
no answer

- August – September 2015 ➔ radiotherapy to the whole spine (46 Gy, 23 fractions) followed by paclitaxel and trastuzumab
- October 2015: reduction of the pain, frequency of urinary incontinence and weakness of legs; spinal MRI: no significant changes; brain MRI: no abnormalities; CSF examination: few inflammatory and atypical cells and protein content stable

Question 2 : which option would you choose?	Number (%)
monitoring with MRI and CSF examinations	43 (19%)

prolongation of systemic chemotherapy	45 (20%)
intrathecal chemotherapy (either methotrexate or liposomal cytarabine)	18 (8%)
other	5 (2%)
answer	113 (51%)

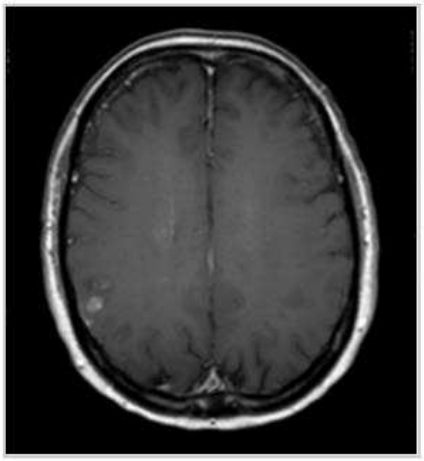
- October 2015 – January 2016: intrathecal liposomal cytarabine (6 injections)
- February 2016: neurologically stable; spinal MRI with mild reduction of enhancing lesions (Fig. B); brain MRI: no abnormalities; CSF examination: no atypical or neoplastic cells and normal protein content

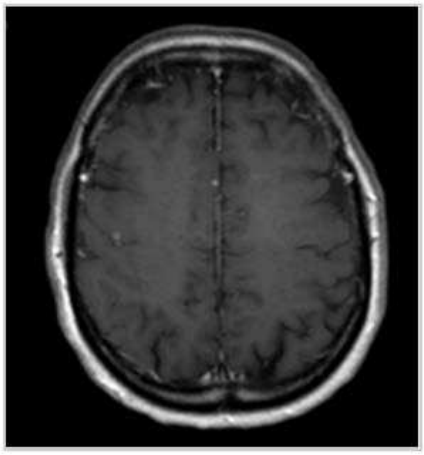
Question 3 : how would you judge the post-treatment MRI findings (Fig. B) in comparison with those of pre-treatment (post-surgery) MRI (Fig. A) ?	Number (%)
minor response (26-49% reduction of enhancing lesions)	35 (15.5%)
partial response (50 or more % reduction of enhancing lesions)	49 (22%)
non significant changes	15 (6.5%)
too difficult for me to evaluate	14 (6.5%)
no answer	111 (49.5%)

Case 5 NON-SMALL CELL LUNG CANCER, EGFR-MUTATED

49 year-old at the time of neurological evaluation

- September 2012 : lung adenocarcinoma, TTF1 positive, EGFR positive (exon 19 deletion), HER2 negative, KRAS negative, BRAF negative, with initially pleural extension (Tx N1 M1b)
- September 2012 : gefitinib (6 months) followed by cisplatin + pemetrexed + gefinitib/placebo after a first lung progression (IMPRESS trial)
- August 2013 : lung progression ➔ docetaxel
- January 2014 : brain and pleural progression ➔ ifosfamide – gemcitabine X 9
- October 2014 : suspicion of leptomeningeal metastases on brain MRI, stable extra-CNS disease. ECOG-PS= 0, but progressive headaches, fluctuant diploplia, mild gait disorder and mild cognitive disorder





Question 1 : how would you complete the neurological evaluation ?	Number (%)
entire spinal MRI	83 (37%)
CSF analysis	74 (33%)
CSF flow study	10 (4.5%)
determination of the EGFR mutation in the CSF	28 (12.5%)
no more examination	4 (2%)
other	2 (1%)
no answer	122 (54.4%)

Question 2 : which option would you recommend for the management of the patient if leptomeningea cytology ?
whole brain radiotherapy
whole brain radiotherapy followed by systemic treatment
whole brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy
stereotactic brain radiotherapy followed by systemic treatment
stereotactic brain radiotherapy followed by systemic treatment and intra-CSF chemotherapy
systemic treatment alone
systemic treatment and intra-CSF chemotherapy
intra-CSF chemotherapy alone
other
no answer

Question 3 : which systemic treatment would you choose if leptomeningeal metastasis was confirmed by positive CSF cytology ?	Number (%)
ifosfamide + gemcitabine	8 (3.5%)
erlotinib	31 (14%)
high-dose gefitinib	6 (2.5%)
afatinib	19 (8.5%)
other	12 (5.5%)
no anwser	148 (66%)

Question 4 : which intra-CSF treatment would you chose if leptomeningeal metastasis was confirmed by positive CSF cytology ?	Number (%)
liposomal cytarabine	33 (14.5%)
methotrexate	24 (10.5%)
thiotepa	5 (2%)
I never use intra-CSF chemotherapy	23 (10%)
other	7 (3%)
no answer	132 (60%)

Case 6 MEDULLOBLASTOMA

22 year-old male

- August 2010 : headache and vomiting ➔ MRI: enhancing tumor in the cerebellum (Fig. A)
- September 2010: Total resection of a medulloblastoma
- October 2010 (at staging before radiotherapy): spine MRI with nodular enhancing lesions in the leptomeninges (Fig. B); brain MRI normal; CSF examination: no neoplastic cells

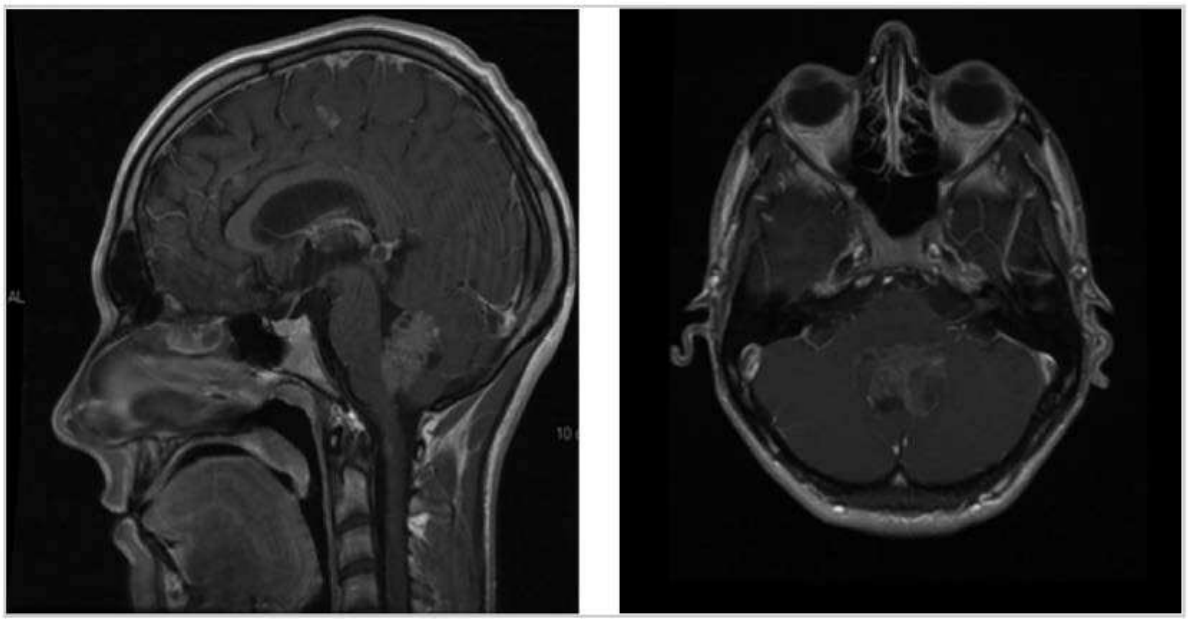


Fig. A

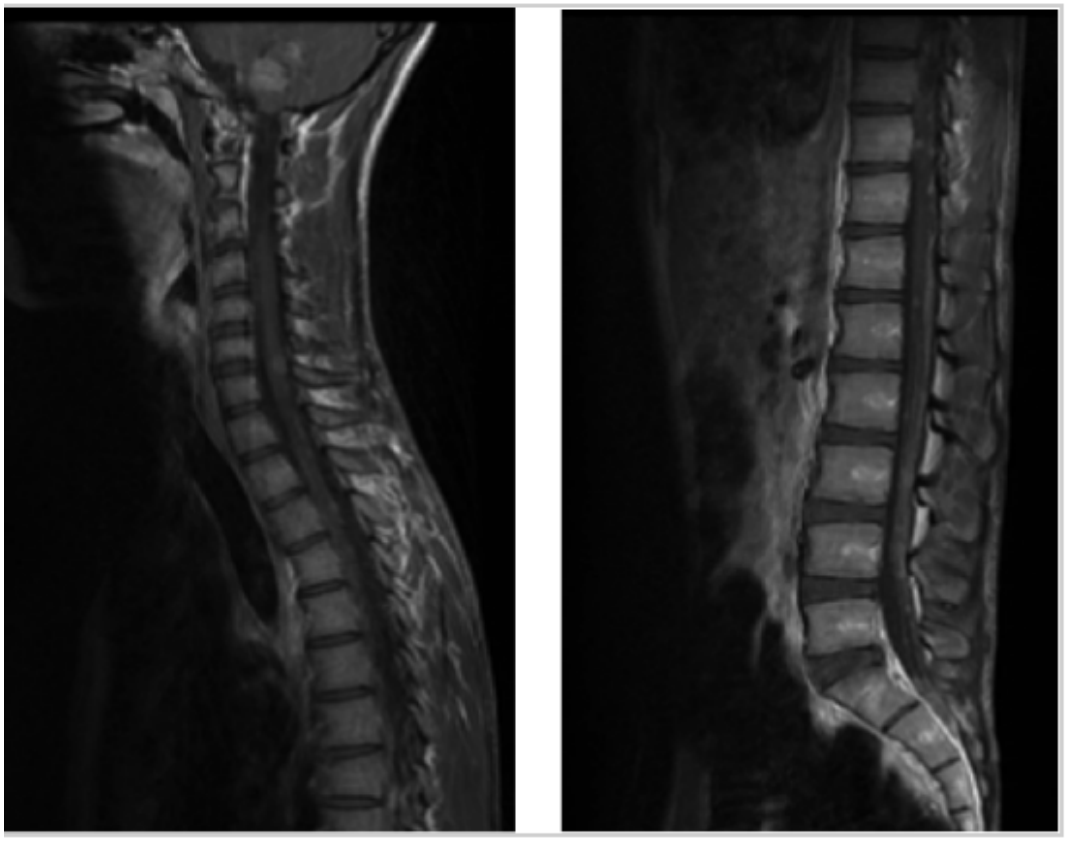


Fig. B

Question 1 : what treatment would you choose?	Number (%)
standard whole CNS radiotherapy with boost to the spinal lesions	17 (7.5%)
standard whole CNS radiotherapy followed by systemic chemotherapy	61 (27%)
standard whole CNS radiotherapy followed by intrathecal chemotherapy	3 (1.5%)
other	11 (5%)
no answer	132 (59%)

Question 2 : in case of systemic chemotherapy which drugs would you choose ?	Number (%)
cisplatin-based chemotherapy	62 (27.5%)
high-dose chemotherapy	24 (10.5%)
other	2 (1%)
no answer	136 (61%)

Question 3 : in case of intrathecal chemotherapy which agent would you choose ?	Number (%)
liposomal cytarabine	22 (10%)
thiotepa	12 (5.5%)
methotrexate	5 (2%)
I never use intra-CSF treatment for medulloblastoma	37 (16.5%)
other	3 (1.5%)
no answer	145 (64.5%)

- Following radiotherapy and intrathecal liposomal cytarabine the patient had a new MRI to evaluate the response (Fig. C)

Fig. C

Question 4 : how would you judge the post-treatment MRI findings (Fig. C) in comparison with those of pretreatment MRI (Fig. B)?	Number (%)
minor response (26-49% reduction of enhancing lesions)	11 (5%)
partial response (50 or more % reduction of enhancing lesions)	61 (27%)
non-significant changes	1 (0.5%)
too difficult for me to evaluate	15 (7%)
no answer	136 (60.5%)

Case 7 GLIOBLASTOMA

23 year-old female

- September 2013: partial complex seizures and headache → MRI: enhancing tumor in the thalamus and upper mesencephalon
- October 2013: partial resection of a glioblastoma (IDH1/2 wild type and MGMT promoter unmethylated)
- November – December 2013: EORTC-NCIC regimen (TMZ/RT → TMZ).
- In late February 2014 : MRI with progressive local disease (Fig. A) and leptomeningeal enhancing lesions (Fig. B), with patient still ambulatory

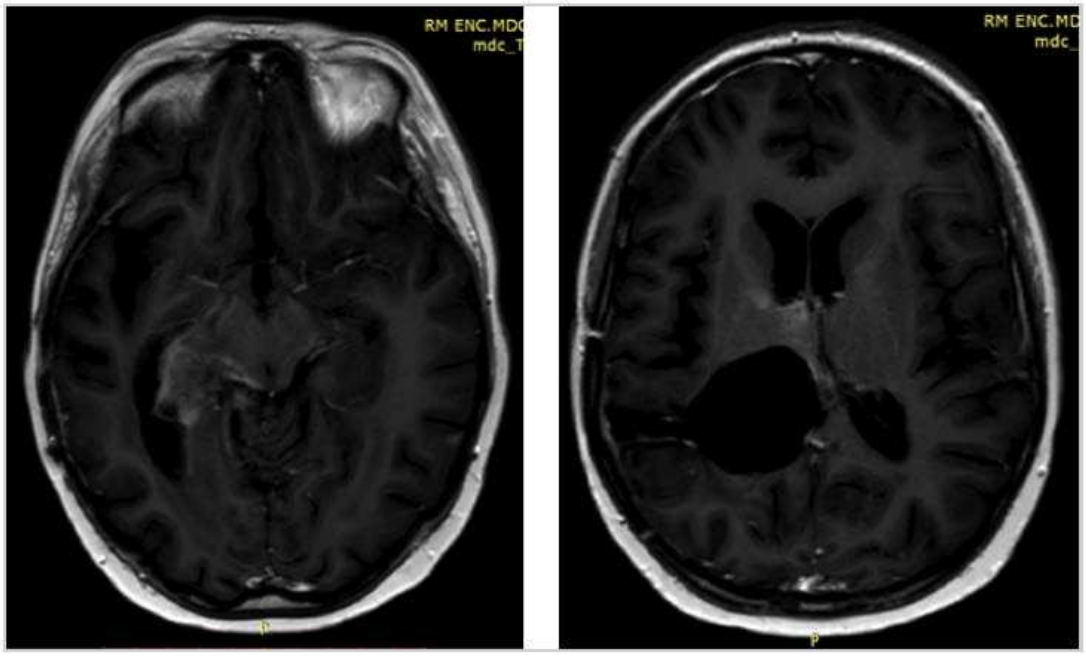


Fig. A

Fig. B

Question 1 : which would be your treatment of choice?	Number (%)
palliative care	5 (2%)
systemic chemotherapy	53 (24%)
intrathecal chemotherapy	3 (1.5%)
radiotherapy of the spinal lesion	30 (13.5%)
other	5 (2%)
no answer	128 (57%)

Question 2 : in case of systemic chemotherapy which drug would you choose?	Number (%)
nitrosourea (CCNU or fotemustine)	60 (27%)
bevacizumab	18 (8%)
dose-dense TMZ	6 (2.5%)
other	4 (2%)
no answer	136 (60.5%)

Case 8 EPENDYMOMA

49 year-old female

- February 2000: vertigo and gait ataxia → MRI: enhancing tumor in the fourth ventricle.
- March 2000: subtotal resection of an ependymoma WHO grade II
- April 2000: MRI: residual tumor in the IV ventricle; spinal MRI normal; CSF examination normal
- April-May 2000 : radiotherapy on the posterior fossa (55 Gy)
- June 2000: MRI with minor response
- September 2000 – January 2009: MRI stable
- October 2009: nodular enhancing lesions on the pons-IV ventricle (Fig. A) and along the spine (Fig. B), but patient neurologically asymptomatic and CSF negative

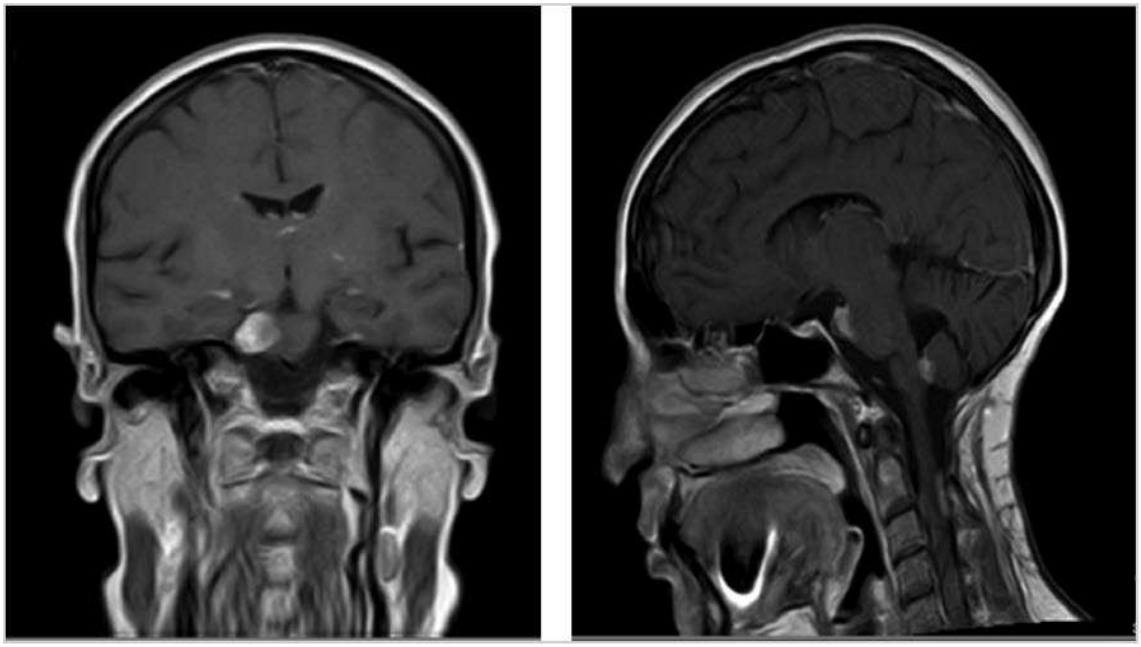


Fig. A

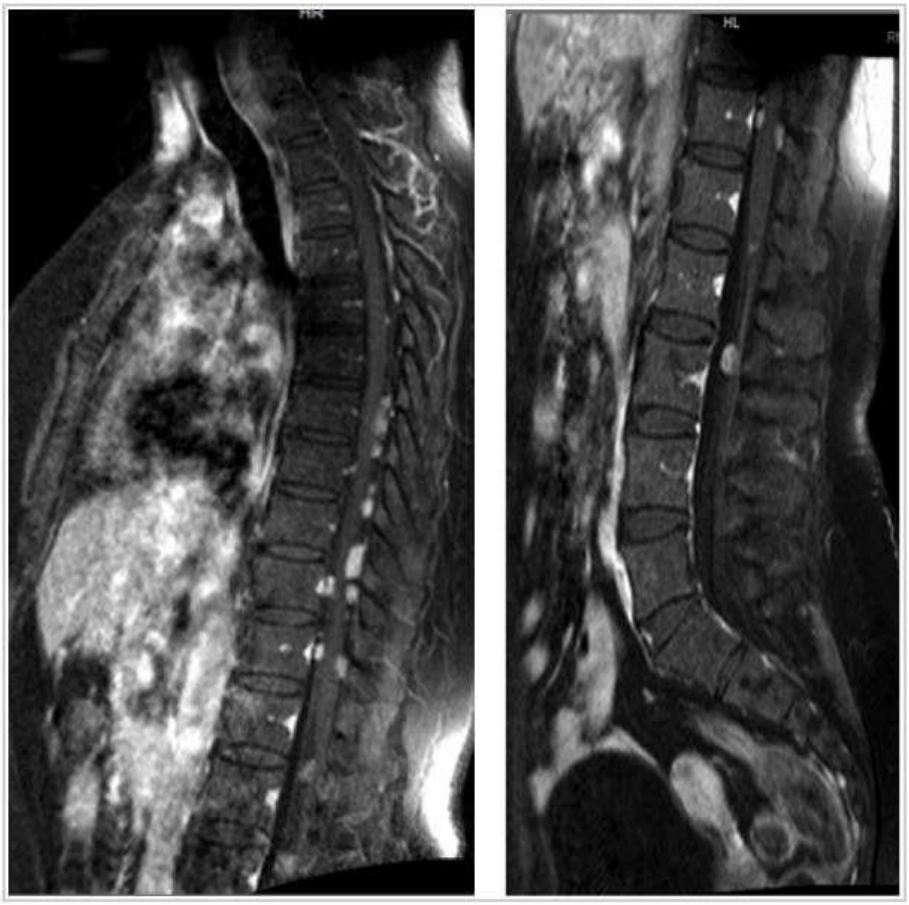
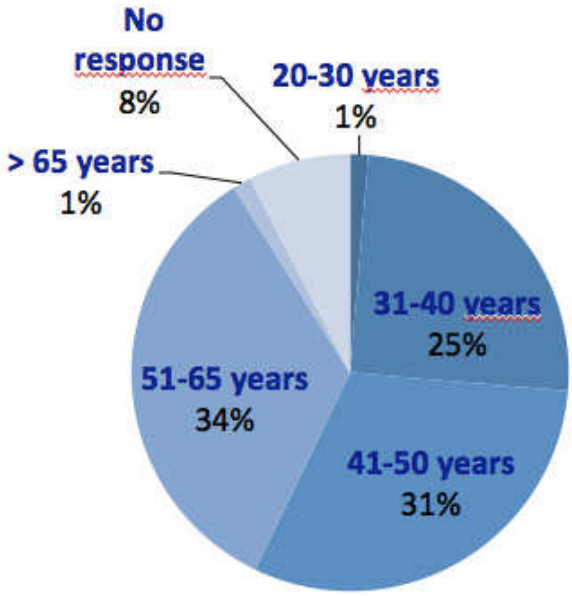


Fig. B

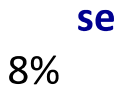
Question 1 : what do you recommend?	Number (%)
observation with MRI until neurological symptoms will develop	18 (8%)
radiotherapy to the whole spine and cyberknife to the nodule in the pons	41 (18.5%)
systemic chemotherapy	15 (6.5%)
intrathecal chemotherapy	0 (0%)
combination of focal radiotherapy and chemotherapy	26 (11.5%)
no answer	124 (55.5%)

Question 2 : if choosing chemotherapy which drug would you use?
cisplatin/carboplatin
temozolomide
intrathecal liposomal cytarabine
other
no answer

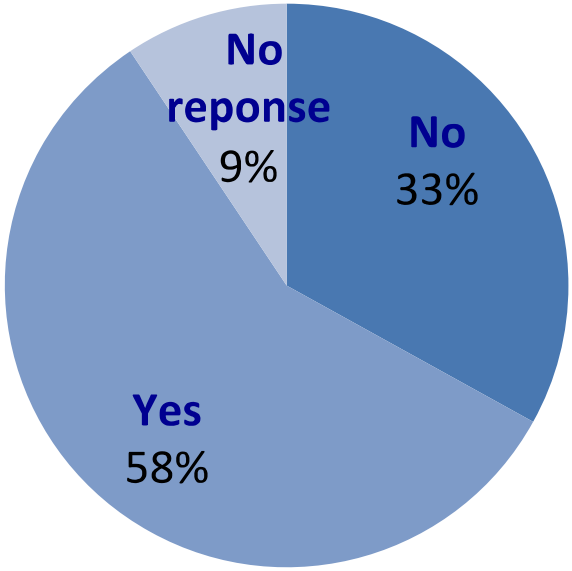
Supplementary Figure 1A : Repartition of physicians according to the age



Supplementary Figure 1B : Repartition of physicians according to the number of patients with suspected LM seen per month



Supplementary Figure 1C : Repartition of physicians according to being in charge or not of LM in their hospital



Supplementary table: Response patterns by age, specialty, being in charge of LM at the center, or seeing 0-1 versus 2 or more patients per month

Significant items				p-values
AGE				
	31-40 (n=54) (n, % of participants)	41-50 (n=69) (n, % of participants)	51-65 (n=78) (n, % of participants)	
Specialty by training (missing: 15)	neurologist: 25 (47%) medical oncologist: 15 (28.5%) radiotherapist: 7 (13%) neurosurgeon: 6 (11.5%)	neurologist: 20 (31%) medical oncologist: 14 (21.5%) radiotherapist: 24 (37%) neurosurgeon: 7 (11%)	neurologist: 26 (38%) medical oncologist: 22 (32.5%) radiotherapist: 11 (16%) neurosurgeon: 9 (13%)	0.0446
Physician in charge of LM diagnosis: medical oncologist (missing data: 0)	yes: 39 (72%) no: 15 (28%)	yes: 35 (50.5%) no: 34 (49.5%)	yes: 45 (57.5%) no: 33 (42.5%)	0.0519
Physician in charge of LM diagnosis: other (missing data: 0)	yes: 1 (2%) no: 53 (98%)	yes: 12 (17.5%) no:57 (82.5%)	yes: 6 (7.5%) no: 72 (92.5%)	0.0111
Physician in charge of LM treatment: other (missing: 0)	yes: 0 (0%) no: 54 (100%)	yes: 9 (13%) no: 60 (87%)	yes: 5 (6.4%) no: 73 (93.5%)	0.0182
CSF analysis performed: always for suspicion of LM from solid tumors except glioma (missing: 0)	yes: 32 (59.5%) no: 22 (40.5%)	yes: 31 (45%) no: 38 (55%)	yes: 61 (78%) no: 17 (22%)	0.0002
CSF analysis performed: always for suspicion of LM from glioma (missing: 0)	yes: 10 (18.%) no: 44 (81.5%)	yes: 5 (7.25%) no: 64 (92.75%)	yes:24 (31%) no: 54 (69%)	0.0015
CSF analysis performed only if doubt after clinical and MRI evaluation for a suspicion of LM from solid tumor (except glioma) (missing: 0)	yes: 22 (40.5%) no: 32 (59%)	yes: 34 (49%) no: 35 (71%)	yes: 18 (23%) no: 60 (77%)	0.0035
a CSF cytology defined as “atypical” is considered as (missing: 15)	positive: 33 (62.5%) negative: 20 (37.5%)	positive: 32 (53.5%) negative: 28 (46.5%)	positive: 31 (42.5%) negative: 42 (57.5%)	0.0852

intra-CSF treatment is always administered for LM (missing: 0)	yes: 0 (0%) no: 54 (100%)		yes: 2 (3%) no: 67 (97%)	yes: 6 (7.5%) no: 72 (92.5%)	0.0720
intra-CSF treatment is never administered for LM (missing: 0)	yes: 3 (5.5%) no: 51 (94.4%)		yes: 1 (19%) no: 56 (81%)	yes: 5 (6.5%) no: 73 (93.5%)	0.0189
intra-CSF treatment is administered for LM depending on CSF and MRI findings (missing: 0)	yes: 29 (73.5%) no: 25 (46.5%)		yes: 22 (32%) no: 47 (68%)	yes: 30 (38.5%) no: 48 (61.5%)	0.0457
intraventricular CSF chemotherapy is preferred over lumbar intra-CSF therapy only in patients with regular CSF flow sudies (missing: 0)	yes: 1 (2%) no: 53 (98%)		yes: 9 (13%) no: 60 (87%)	yes: 5 (6.5%) no: 73 (93.5%)	0.0579
whole brain radiation therapy is performed in case of concomitant brain metastases (missing: 0)	yes: 6 (11%) no: 48 (89%)		yes: 17 (24.5%) no: 52 (75.5%)	yes: 11 (14%) no: 67 (85%)	0.0972
SPECIALTY BY TRAINING					
	neurologist (n=77) (n, % of participants)	medical oncologist (n=52) (n, % of participants)	radiotherapist (n=42) (n, % of participants)	neurosurgeon (n=23) (n, % of participants)	
Physician in charge of LM at hospital (missing: 36)	yes: 58 (79.5%) no: 15 (20.5%)	yes: 31 (61%) no: 20 (39%)	yes: 23 (55%) no: 19 (45%)	yes: 11 (50%) no: 11 (50%)	0.0104
Physician in charge of the diagnosis of LM: medical oncologist (missing: 30)	yes: 38 (49.5%) no: 39 (50.5%)	yes: 45 (86.5%) no: 7 (13.5%)	yes: 22 (52.5%) no: 20 (47.5%)	yes: 12 (52%) no: 11 (48%)	0.0001
Physician in charge of the diagnosis of LM: neurologist (missing: 30)	yes: 68 (88%) no: 9 (12%)	yes: 15 (29%) no: 37 (71%)	yes: 12 (28.5%) no 30 (71.5%)	yes: 5 (21.5%) no: 18 (78%)	<0.0001
Physician in charge of the diagnosis of LM: radiotherapist (missing: 30)	yes: 9 (11.5%) no: 68 (88%)	yes: 9 (17.5%) no: 43 (82.5%)	yes: 18 (43%) no: 24 (57%)	yes: 10 (43.5%) no: 13 (56.5%)	<0.0001
Physician in charge of the diagnosis of LM: neurosurgeon (missing: 30)	yes: 6 (8%) no: 71 (92%)	yes:10 (19%) no: 42 (81%)	yes: 7 (16.5%) no: 35 (83.5%)	yes: 14 (61%) no: 9 (39%)	<0.0001
Physician in charge of the diagnosis of LM: other	yes: 1 (1.50%) no: 76 (98.5%)	yes: 5 (9.5%) no: 47 (90%)	yes: 7 (16.5%) no: 35 (83.5%)	yes: 3 (13%) no: 20 (87%)	0.0215

(missing: 30)					
Physician in charge of the treatment of LM: medical oncologist (missing: 30)	yes: 47 (61%) no: 30 (39%)	yes: 47 (90.5%) no: 5 (9.5%)	yes: 25 (59.5%) no: 17 (40.5%)	yes: 16 (69.5%) no: 7 (30.5%)	0.0016
Physician in charge of the treatment of LM: neurologist (missing: 30)	yes: 57 (74%) no: 20 (26%)	yes: 3 (6%) no: 49 (94%)	yes: 5 (12%) no: 37 (88%)	yes: 4 (17.5%) no: 19 (82.5%)	<0.0001
Physician in charge of the treatment of LM: radiotherapist (missing: 30)	yes: 20 (26%) no: 57 (74%)	yes: 12 (23%) no: 40 (77%)	yes: 28 (67%) no: 14 (33.5%)	yes: 9 (39%) no: 14 (61%)	<0.0001
Physician in charge of the treatment of LM: neurosurgeon (missing: 30)	yes: 6 (8%) no: 71 (92%)	yes: 2 (4%) no: 50 (96%)	yes: 3 (7%) no: 39 (93%)	yes: 11 (48%) no: 12 (52%)	<0.0001
Physician in charge of the treatment of LM: other (missing: 30)	yes: 1 (1.5%) no: 76 (98.5%)	yes: 4 (7.5%) no: 48 (92.5%)	yes: 4 (7.5%) no: 38 (90.5%)	yes: 0 (0%) no: 23 (100%)	0.0928
CSF analysis always performed in case of suspicion of LM from solid tumors (except glioma) (missing: 30)	yes: 47 (61%) no: 30 (39%)	yes: 41 (79%) no: 11 (21%)	yes: 11 (26%) no: 31 (74%)	yes: 14 (61%) no: 9 (39%)	<0.0001
CSF analysis always performed in case of suspicion of LM from glioma (missing: 30)	yes: 13 (17%) no: 64 (83%)	yes: 14 (23%) no: 38 (73%)	yes: 2 (5%) no: 40 (95%)	yes: 4 (17%) no: 19 (82.5%)	0.0443
CSF analysis performed in case of suspicion of LM from solid tumors (except glioma) in case of doubt after clinical and MRI evaluations (missing: 30)	yes: 27 (35%) no: 50 (65%)	yes: 11 (21%) no: 41 (79%)	yes: 29 (69%) no: 13 (31%)	yes: 7 (30.5%) no: 16 (69.5%)	<0.0001
CSF analysis performed in case of suspicion of LM from glioma in case of doubt after clinical and MRI evaluations (missing: 30)	yes: 24 (31%) no: 53 (69%)	yes: 3 (7%) no 49 (94%)	yes: 7 (16.5%) no: 35 (83.5%)	yes: 3 (13%) no: 20 (87%)	0.0030
CSF flow study always performed at LM diagnosis (missing:30)	yes: 9 (11.5%) no: 68 (88%)	yes: 13 (25%) no: 39 (75%)	yes: 5 (12%) no 37 (88%)	yes: 7 (30.5%) no: 16 (69.5%)	0.0603
Median volume of CSF sample (missing 42)	>10 ml: 23 (31%) 5-10 ml: 38 (51.5%)	>10 ml: 9 (18%) 5-10 ml: 17 (34%)	>10 ml: 1 (3%) 5-10 ml: 12 (54.5%)	>10 ml: 1 (1.5%) 5-10 ml: 0 (0%)	0.0006

	2-5 ml: 12 (16%) 0-2 ml: 1 (1.5%)	2-5 ml: 24 (48%) 0-2 ml: 0 (0%)	2-5 ml: 6 (27.5%) 0-2 ml: 2 (5.5%)	2-5 ml: 2 (5.5%) 0-2 ml: 0 (0%)	
Median time between CSF sampling and processing (missing:44)	<30 min: 21 (29.5%) 30-60 min: 27 (38%) 60-90 min: 15 (21%) >90 min: 8 (11.5%)	<30 min: 7 (14%) 30-60 min: 29 (58%) 60-90 min: 12 (24%) >90 min: 2 (4%)	<30 min: 3 (8%) 30-60 min: 18 (47.5%) 60-90 min: 12 (31.5%) >90 min: 5 (13%)	<30 min: 3 (14.5%) 30-60 min: 18 (47.5%) 60-90 min: 4 (19%) >90 min: 4 (19%)	0.0847
positive CSF cytology always required for LM diagnosis (missing: 37)	yes: 6 (8%) no: 68 (92%)	yes: 4 (8%) no: 47 (92%)	yes: 5 (13%) no: 34 (87%)	yes: 6 (26%) no: 17 (74%)	0.0896
Systemic treatment always administered for LM (when feasible) missing: 30	yes: 17 (22%) no: 60 (73%)	yes: 26 (50%) no: 26 (50%)	yes: 11 (26%) no: 31 (74%)	yes: 11 (48%) no: 12 (52%)	0.0029
Intra-CSF treatment always administered for LM (missing 30)	yes: 6 (8%) no: 71 (92%)	yes: 0 (0%) no: 52 (100%)	yes: 0 (0%) no: 42 (100%)	yes: 1 (4.5%) no: 22 (95.5%)	0.0594
Intra-CSF treatment depending on CSF and MRI characteristics (missing: 30)	yes: 36 (47%) no: 41 (53%)	yes: 22 (42%) no: 30 (57.5%)	yes: 9 (21.5%) no:33 (78.5%)	yes: 7 (30.5%) no: 16 (69.5%)	0.0392
Intra-CSF treatment administered depending on the primary cancer (missing: 30)	yes: 51 (66%) no: 26 (34%)	yes: 37 (71%) no: 15 (29%)	yes: 23 (55%) no: 19 (45%)	yes: 10 (43.5%) no: 13 (56.5%)	0.0809
Intra-CSF treatment administered only in combination with a systemic treatment (missing: 30)	yes: 2 (2.5%) no: 75 (97.5%)	yes: 3 (6%) no: 49 (94%)	yes: 2 (5%) no: 40 (95%)	yes: 4 (17.5%) no: 19 (82.5%)	0.0620
Intraventricular intra-CSF treatment is preferred on intralumbar intra-CSf treatment only if lumbar punctures are not feasible (missing: 30)	yes: 40 (52%) no: 37 (48%)	yes: 34 (65.5%) no: 18 (34.5%)	yes: 16 (38%) no: 26 (62%)	yes: 10 (43.5%) no: 13 (56.5%)	0.0542
WBRT always performed for LM treatment (missing: 30)	yes: 11 (14.5%) no: 66 (86%)	yes: 2 (4%) no: 50 (96%)	yes: 12 (28.5%) no: 30 (71.5%)	yes: 8 (35%) no: 15 (65%)	0.0012
WBRT performed in case of concomitant brain metastases (missing: 30)	yes: 43 (56%) no: 34 (44%)	yes: 32 (61.5%) no: 20 (38.5%)	yes: 18 (43%) no: 24 (57%)	yes: 8 (35%) no: 15 (65%)	0.0901
WBRT performed in case of multifocal nodular/bulky LM	yes: 43 (56%) no: 34 (44%)	yes: 38 (73%) no: 14 (27%)	yes: 21 (50%) no: 21 (50%)	yes: 9 (39%) no: 14 (61%)	0.0248

(missing 30)					
Focal RT based on neurological symptoms associated with MRI abnormalities only (missing: 30)	yes: 55 (71.5%) no: 45 (86.5%)	yes: 45 (86.5%) no: 7 (13.5%)	yes: 38 (90.5%) no: 4 (9.5%)	yes: 17 (74%) no: 6 (26%)	0.0401
Change of steroids dose part of criteria for LM response assessment (missing: 36)	yes: 37 (50.5%) no: 36 (49.5%)	yes: 42 (81%) no: 10 (19%)	yes: 25 (62.5%) no: 15 (37.5%)	yes: 13 (56.5%) no: 10 (43.5%)	0.0071
PHYSICIAN IN CHARGE OF LM IN THE CENTER VERSUS PHYSICIAN NOT IN CHARGE IN ITS CENTER					
	Participants declared as being the neuro-oncologist in charge (n=129) (n, % of participants)		Participants declared as not being the neuro-oncologist in charge (n=74) (n, % of participants)		
Specialty of the participants (missing: 36)	neurologist: 58 (47%) medical oncologist: 31 (25%) radiation oncologist: 23 (18.5%) neurosurgeon: 11 (9%)		neurologist: 15 (23%) medical oncologist: 20 (31%) radiation oncologist: 19 (29%) neurosurgeon: 11 (17%)		0.0104
Physician in charge of the diagnosis of LM: medical oncologist (missing: 21)	yes: 68 (52.5%) no: 61 (47.5%)		yes: 51 (69%) no: 23 (31%)		0.0240
Physician in charge of the diagnosis of LM: neurologist (missing: 21)	yes: 74 (57.5%) no: 55 (42.5%)		yes: 31 (42%) no: 43 (58%)		0.0337
Physician in charge of the diagnosis of LM: neurosurgeon (missing: 21)	yes: 30 (23%) no: 99 (76.5%)		yes: 10 (13.5%) no: 64 (86.5%)		0.0930
Physician in charge of the treatment of LM: medical oncologist (missing: 21)	yes: 80 (62%) no: 49 (38%)		yes: 58 (78.5%) no: 16 (21.5%)		0.0162
Physician in charge of the treatment of LM: neurologist (missing: 21)	yes: 55 (42.5%) no: 74 (57.36)		yes: 15 (20.5%) no: 59 (79.5%)		0.0013
Physician in charge of the treatment of LM: other (missing: 21)	yes: 6 (4.5%) no: 123 (95.5%)		yes: 8 (11%) no: 66 (89%)		0.0955
Standardized scale available (missing: 25)	yes: 28 (21.5%) no: 101 (78.5%)		yes: 8 (11.5%) no: 62 (88.5%)		0.0721
CSF flow study always performed at	yes: 17 (13%)		yes: 18 (24.5%)		0.0430

LM diagnosis (missing: 21)	no: 112 (87%)	no: 56 (75.5%)	
Median CSF volume collected for CSF cytology at LM diagnosis (missing:31)	>10 ml: 26 (20.5%) 5-10 ml: 61 (48%) 2-5 ml: 37 (29%) 0-2 ml: 3 (2.5%)	>10 ml: 13 (19.5%) 5-10 ml: 23 (35%) 2-5 ml: 30 (45.5%) 0-2 ml: 0 (0%)	0.0844
A CSF cytology defined as suspicious is considered as (missing: 31)	positive: 112 (89%) negative: 14 (11%)	positive: 53 (79%) negative: 14 (21%)	0.0661
Intraventricular intra-CSF chemotherapy is preferred over intralumbar intra-CSF chemotherapy for most patients (missing: 21)	yes: 40 (31%) no: 89 (69%)	yes: 9 (12%) no: 65 (88%)	0,0025
Frequency of MRI examination during follow-up (missing: 28)	every 2 months: 19 (14.5%) every 2 months initially, then every 3 months: 40 (31%) every 3 months: 37 (28.5%) only depending on the clinical course: 33 (25.5%)	every 2 months: 10 (15%) every 2 months initially, then every 3 months: 13 (19.5%) every 3 months: 14 (21%) only depending on the clinical course: 30 (45%)	0.0406
PHYSICIAN IN CHARGE OF >2 LM PATIENTS PER MON TH VERSUS PHYSICIAN IN CHARGE OF 0-2 LM PATIENTS PER MONTH			
	At least 2 LM patients per month (n=88) (n, % of participants)	0-1 LM patients per month (n=119) (n, % of participants)	
Physician in charge of LM patient at hospital (missing: 21)	yes: 65 (75.5%) no: 21 (24.5%)	yes: 64 (54.5%) no: 53 (45.5%)	0.0023
Physician in charge of LM treatment: medical oncologist (missing:18)	yes: 53 (61%) no: 34 (39%)	yes: 88 (74%) no: 31 (26%)	0.0468
Physician in charge of LM treatment: neurologist (missing:18)	yes: 36 (41.5%) no: 51 (58.5%)	yes: 35 (29.5%) no: 84 (70.5%)	0.0742
In case of negative CSF cytology, a combination of clinical and radiological signs is considered sufficient to diagnose LM (missing: 22)	yes: 83 (97.5%) no: 2 (2.5%)	yes: 108 (92.5%) no: 9 (7.5%)	0.0987
Intraventricular intra-CSF is preferred over intralumbar chemotherapy in most	yes: 27 (31%) no: 60 (69%)	yes: 23 (19.5%) no: 96 (80.5%)	0.0529

patients (missing: 18)			
Intraventricular intraCSF chemotherapy is preferred over intralumbar intraCSF if repeated lumbar punctures are not feasible (missing: 18)	37 (42.5%) 50 (57.5%)	66 (55.5%) 53 (44.4%)	0.0667